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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 10/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/267,456	MOSCA ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2003* .

2a)☒ This action is **FINAL.** 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *37-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's Amendment and Remarks, filed 7/14/03, are acknowledged.

2. Claims 1-36 have been canceled.
Claims 37-59 are pending and being acted upon.

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Newly added Claims 37-59 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that after contacting mesenchymal stem cells (MSCs) *in vitro* with an antigen, the MSCs of the claimed method would process said antigen into an antigen fragment for presentation by said MSCs, for the reasons of record as set forth previously in papers mailed 2/28/02, 9/19/02, and 4/24/03.

Applicant's arguments, filed 7/14/03, have been fully considered but they are not persuasive. Applicant argues that Example 1 of the specification demonstrates "that mesenchymal stem cells, which do not produce co-stimulatory molecules in a sufficient amount to activate T-cells, can process and present antigens or fragments to T-cells in order to induce tolerance to such antigens."

Applicant's argument appears to be factually inaccurate. First, Example 1 does not show that mesenchymal stem cells can process antigen - the example is silent on said processing. Second, the example also fails to show T cell tolerance, the example simply shows modest inhibition of T cell proliferation in a highly artificial *in vitro* model.

Applicant argues that "The Examiner's reliance on Paul, like his previous reliance on Janeway, is misguided."

It remains the Examiner's position that the references, particularly Paul (considered by immunologists to be the preeminent immunology textbook), show the state of the art regarding antigen presenting cells (APCs). The very fact that mesenchymal stem cells are not recognized in the references as APCs demonstrates that mesenchymal stem cells are not recognized by those skilled in the art as APCs. As set forth in the first line of the Summary of the Invention, it is Applicant's discovery that "mesenchymal stem cells can be used to deliver antigens to the immune system such that an immune response to the antigen will be inhibited, i.e eliminated, reduced or ameliorated." It is this nonobvious discovery that would render the invention patentable.

Applicant argues "The Examiner is taking the position that Applicants must demonstrate that MSCs are capable of antigen processing, and that because Applicants have not made such a demonstration, the claims are not enabled... The Examiner is reminded that the burden is not upon Applicants to show enablement, but is upon the Examiner to show that the claims are not enabled."

It remains the Examiner's position that the references teach the state of the art, i.e., that certain cell types, e.g., dendritic cells, are recognized as being able to process and present antigen, whereas most other cell types are not. Applicant's claim that mesenchymal stem cells also possess the ability to process antigen is counter to that which is art recognized. Accordingly, *some* demonstration of said processing is required. No such demonstration has been has been disclosed.

Note that the Examiner has conceded that mesenchymal stem cells can present antigen in the context set forth in Example 1, however, antigen presentation is not antigen processing, i.e., the result (presentation) demonstrates nothing as regards the mechanism by which the result is achieved (processing).

5. The following is a new ground of rejection.

6. Claims 53-59 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of "A method of inducing T cell tolerance" in Claim 53.

Applicant's amendment, filed 7/14/03, fails to assert that no new matter has been introduced into the claims and no support for the new limitations has been found in the specification.

7. Claims 53-59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:
a method of inhibiting a T cell response to an antigen,
does not reasonably provide enablement for:
a method of inducing T cell tolerance.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention.

Immunologically, "tolerance" comprises much more than mere inhibition of an immune response. As set forth in *Fundamental Immunology* (1999), Ron Schwartz (a well recognized expert in tolerance) teaches,

"I define tolerance as a physiologic state in which the immune system does not react destructively against the components of an organism that harbors it or against antigens that are introduced to it."

Clearly then, tolerance is an *in vivo* process. Regarding *in vivo* methods, said methods generally rely on unpredictable mechanisms, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less

information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)" The MPEP further states that physiological activity can be considered inherently unpredictable. The state of the biological arts are such that mesenchymal stem cells are not recognized as being capable of inducing tolerance, thus the claimed method would be considered to be highly unpredictable.

The specification discloses no methods of inducing tolerance. Indeed, Example 1 actually shows only a modest inhibition of T cell proliferation in a highly artificial *in vitro* model. This is clearly not tolerance. Accordingly, the induction of immune tolerance by the claimed method must be considered to be highly unpredictable and requiring of undue experimentation.

In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Thus, in view of the quantity of experimentation necessary, the lack of *in vivo* working examples of tolerance induction, the unpredictability of the art, and the lack of sufficient guidance in the brief specification, it would take undue trials and errors to practice the claimed invention.

8. No claim is allowed.

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805 The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. **Please Note**: inquiries of a general nature or relating to the status of this application should not be directed to the Examiner but rather should be directed to the Technology Center 1600 Customer Service Center at (703) 308-0198.

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
October 14, 2003